Telocytes in the female reproductive system: An overview of up-to-date knowledge

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Abstract

Telocytes are emerging cell population localized in the stroma of numerous organs, characterized by a distinctive morphology – small cell body with very long, slender prolongations, termed telopodes. Those cells can be found in the whole female reproductive system: in the vagina, uterus, oviducts and ovaries, mammary glands and also in the placenta. In our review, we aim at complete and transparent revision of the current knowledge of telocytes' localization and function, enriched by the analysis of the possible future direction of development of their clinical applications. The function of telocytes in the reproductive system has not been fully elucidated yet; however, many researchers point at their role in the regulation of local microenvironment, myogenic contractile mechanism, bioelectrical signaling, immunomodulation and regulation of blood flow. Additionally, previous research suggests that telocytes might act as sex hormone level sensors and are connected with pregnancy maintenance. As the morphology and number of those cells change under pathological conditions, such as pre-eclampsia, endometriosis and ovarian failure, there is a chance that they may contribute to therapy of abovementioned conditions. The impact of telocytes on stem cells and angiogenesis has been proven in many organs, and may be useful in regenerative medicine of the female reproductive system. A recently found connection between the proliferation rate of breast cancer cells and stromal cells like telocytes might be a step forward to the management of mammary gland neoplasms.

Key words: ovary, uterus, placenta, telocytes, telopodes

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Introduction

Definition

Telocytes (TCs) are a new type of cells located in the stroma of several organs. Their most characteristic feature is the presence of extraordinarily long, slight prolongations called telopodes (Tps).[1] As far as the female reproductive system is concerned, TCs were described in the mammary gland, vagina, uterus, uterine tube, and placenta.[2–6]

A brief history

The history of TCs derives from Interstitial Cajal Cells (ICCs) discovered by the Spanish neuroanatomist and Nobel Prize winner Santiago Ramon y Cajal. In 1889, Cajal found a new type of cells located within the muscle layer of the intestine, between nerve ganglia and smooth muscle cells.[1]

About a half a century later, Faussone-Pellegrini et al. proved the existence of cells similar to ICCs in the gastrointestinal tract with the use of electron microscopy.[7] In 2005, Popescu et al. found interstitial cells resembling ICCs in the specimens from a mammary gland.[2] They called them Interstitial Cajal-like Cells (ICLCs). A re-examination of the muscular coat of the gut performed by Pieri et al. showed that ICLCs are functionally and morphologically different from ICCs.[8] As a result of these studies, in 2010 Popescu suggested that the name "Interstitial Cajal-like Cells" should be changed to "Telocytes" to clearly distinguish these 2 cell populations.

In the female reproductive system, TCs were first described in 2005, and they were found within the wall of the uterus.[4,9] Further research proved their existence also in the vagina, uterine tubes and placenta (Fig. 1).[3,6,10]

The name "Telocytes" derives from ancient Greek – the word "telos" refers the object of huge potential.[11] Nowadays, thanks to TCs' morphology and functions, they arouse huge interest among researchers as potential contributors to intercellular communication, cancerogenesis and a target for regenerative medicine purposes.[12–14] In our review, we are trying to summarize the current knowledge of tissue distribution, identification methods and potential functions of TCs in female reproductive system.

General aspects of telocytes

Cell phenotype

TCs are small cells with 1–5 long and thin prolongations named telopodes (Tps).[11] The cell body is rather small, its average length oscillates around 9.39 ±3.26 μm. It contains big, heterochromatic nucleus and a thin, perinuclear rim of cytoplasm including few organelles, mainly mitochondria.[11,15] The shape of the cell body is influenced by the actual number of Tps, ranging from piriform, through spindle and triangular to stellate.[16] Tps are up to 1000 μm long, which makes them one of the longest structures in the body, except for some axons.[15,17] As they are composed of dilated segments, named podoms, and thin podomeres, their shape is termed as moniliform.[15,16] Podoms contain organelles responsible for protein synthesis and intercellular signaling, namely rough and smooth endoplasmic reticulum, Golgi apparatus, mitochondria, and caveolae.[12,16] Considering the small size of TCs' body and even more narrow Tps (around 0.5 μm wide podoms), it would be utterly difficult to distinguish them from other cells in light microscopy, thus the golden standard for identifying TCs is transmission electron microscopy (TEM).[16,18]

Localization

Until now, TCs have been identified in the female reproductive system, placenta, mammary gland, cardiovascular system, urinary system, gastrointestinal tract, liver and pancreas, trachea, lungs and pleura, spleen, bone marrow, dura mater, choroid plexus, meninges, trigeminal ganglion, testicles and prostate, skin, skeletal muscles, and eyes.[16,19]

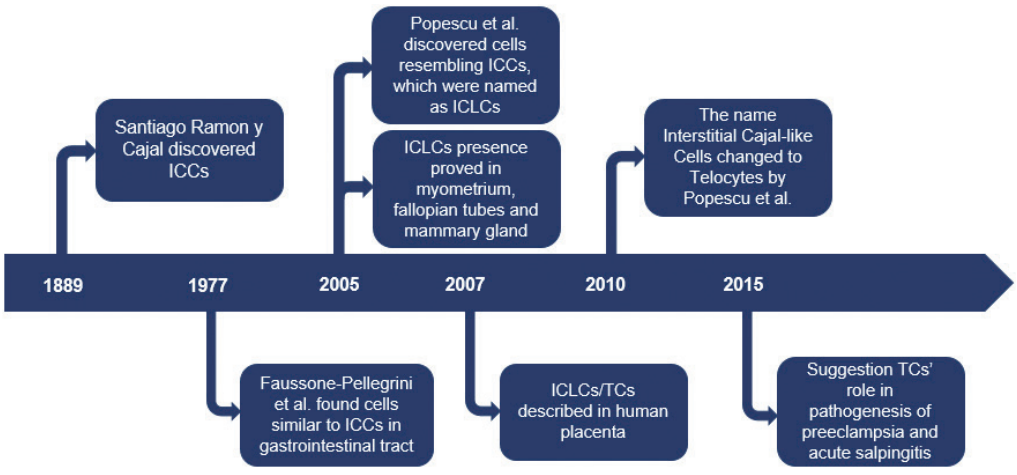

Fig. 1. A timeline of key discoveries in telocytes' research

Cell immunophenotype

Since numerous cells, for instance fibroblasts, neurons or pericytes, have a morphology closely resembling that of telocyte, it became apparent that there is a need for finding specific markers for TCs. Until now, TCs have been confirmed for expression of CD34, c-Kit, vimentin, PDGFR-α and -β, caveolin-1, CD44, Sca-1, Nanog and Oct4.[16,17,20]

Nevertheless, those markers are not perfect. There are a lot of discrepancies between studies in terms of CD34 and c-Kit expression in TCs in different tissues. From all abovementioned markers, CD34 is considered as the most reliable for TCs, although Suciu et al. reported that only 70% of the cells in the placenta, which have TC's morphology, express CD34.[20,21] Moreover, the second most frequently used marker, c-Kit, is not expressed by TCs in gastrointestinal tract.[22] That inconsistency might be caused by imperfections in technical procedures or the existence of tissue-specific subtypes of TCs.[18,21] Another difficulty is connected with the expression of those markers in cells with similar morphology – CD34 is expressed by endoneurial fibroblasts, while vimentin together with PDGFR-β are present in fibroblasts, pericytes and neurons.[18] In order to minimize the risk of misidentification, at least double immunofluorescence staining should be used in order to detect TCs. All things considered, a universal marker for TCs should be found – expressed in every tissue and characteristic only for them.

Intercellular communication

TCs establish both homo- and heterocellular junctions together with connections with extracellular matrix.[20] Moreover, they also communicate through extracellular vesicles, which is a form of juxtacrine/paracrine signaling.[23]

Homocellular junctions are formed between 2 Tps or between Tps and TC's body.[24] In most cases, they are connected by simple apposition of 2 plasma membranes, but there also exist more complex forms of linkage – puncta adhaerentia minima, processus adhaerens, recessus adhaerens, and manubria adhaerentiva. Their primary function is to maintain the integrity of 3-dimensional network of TCs during changes of shape of the tissue. Second presumptive function is linked with catenins, which are important components of adherens junctions, as they might play role in mechanosensing. The last type of homocellular contact is gap junction (nexus), which allows the exchange of ions and small molecules between adjacent cells.[20]

Heterocellular junctions typically have the morphology of point contacts, nanocontacts, planar contacts or simple apposition of plasma membranes.[20] TCs are connected through them with fibroblasts, myofibroblasts, pericytes, endothelial cell, neurons, stem cells, macrophages, mast cells, lymphocytes, plasma cells, Schwann cells, cardiomyocytes and smooth muscle cells.[16,21,24,25] Distinctive type of heterocellular junctions is stromal synapse, which links TCs with immune cells and cardiac stem cells.[24,26]

Extracellular vesicles shedded by TCs can be divided into 3 groups: exosomes (from endosomes), ectosomes (from plasma membrane) and multivesicular cargo (multiple, tightly packed endomembrane-derived vesicles).[23] Vesicles mainly contain proteins, lipids, miRNAs, mRNAs, and mtDNA.[12] Hence, they are crucial for intercellular signaling and they even might be connected with a modification of the post-transcriptional activity of recipient cells.[27] Fibronexuses and focal adhesions were found between TCs and components of extracellular matrix.[20]

Electrophysiological properties of telocytes

Since TCs form an abundant network interconnecting numerous types of cells in the interstitium, a hypothesis was postulated that TCs may be involved in bioelectrical signaling. Thus far, it has been confirmed that TCs express: T-type calcium channels ($Ca_v3.1$ and $Ca_v3.2$), small-conductance calcium-activated potassium channels (SK3), large-conductance calcium-activated potassium channels (BK_{Ca}), inwardly rectifying potassium channels (IK_{ir}) and calcium-dependent hyperpolarisation-activated chloride inward channels.[28,29,30,31]

L-type calcium channels, transient outward potassium channels (I_{to}) and ATP-sensitive potassium channels (K_{ATP}) were not detected in TCs in previous studies.[30,31]

Physiological functions of telocytes

At the present moment, TCs are considered as cells with a rather mysterious function, as there is still a lack of direct evidence for their actual properties. The most frequently proposed one is connected with their role in intercellular signaling – they might be responsible for the integration of signals from numerous systems (for instance nervous, vascular, and immune), regulation of tissue homeostasis and long distance communication including bioelectrical signaling.[16,32] Secondly, since it is proven that TCs are located in close proximity to stem cells, they may be crucial for tissue regeneration and repair.[33] Moreover, TCs build a scaffold, which probably enables the maintenance of proper organization of extracellular matrix and cell migration, also during organogenesis process.[34,35] Additionally, TCs presumably have angiogenic properties thanks to vascular endothelial growth factor (VEGF) expression and they may be vital to anti-oxidative protection, as they are abundant in mitochondrial superoxide dismutase (SOD2).[36,37]

Telocytes in female reproductive system

Telocytes in vagina

Proto-oncogene c-Kit positive cells with long processes, which nowadays might be classified as TCs, were found in muscular layer of the human vagina. Shafik et al. suggested their potential role in generating slow waves resulting in the contractility of smooth muscle cells in the vagina.[3] However, their presence and role in that organ should be thoroughly assessed in the future.

Telocytes in uterus

In the human uterus, TCs were observed in the interstitial space of the endometrium and myometrium.[38,39] Endometrial TCs were detected in the stroma of the stratum functionalis and stratum basalis around the endometrial glands, while myometrial TCs form a 3-dimensional network intermingling with smooth muscle bundles.[1,38] That location in the myometrium may suggest that TCs might be involved in myogenic contractile mechanism during sperm transport prior to fertilization, embryo implantation and delivery.[1]

The quantity of TCs in the endometrium and the myometrium correlates with the reproductive state.[40] Immature rat uteruses present the lowest density of TCs compared to pregnant and postpartum ones.[41] The number of endometrial TCs in pregnant state increases, while there is a reduction of their number in the myometrium.[40] Hence, changes in the quantity of TCs in the myometrium may be associated with the prevention of preterm delivery.[25] Moreover, the highest number of myometrial TCs were found in the postpartum uteri, which may be related with its involution.[40]

Additionally, the morphology of Tps is different in pregnant and non-pregnant myometrium – in non-pregnant uterus podomers are wider and podoms are thinner compared to pregnant ones (Table 1).[31]

The most useful markers used for the identification of TCs in the uterus are CD34 and PDGFR-α/PDGFR-β in double immunolabelling.[25] PDGFR-α/β is mostly expressed at TC's cell body, while Tps are intensely positive for CD34.[28] TCs in uterus are also positive for α-SMA, CD44, vimentin, Sca-1, and c-Kit.[41] Nevertheless, the expression of c-Kit here is questionable. Yang et al. detected various types of TCs in uterine samples: c-Kit(–)/vimentin(+), c-Kit(+)/vimentin(+) and c-Kit(+)/CD34(+). As a consequence, they suggested the presence of various subpopulations of TCs in uterus which may perform disparate functions.[42]

The comparison of markers applicable to the detection of TCs in female reproductive system is shown in Table 2. TCs also express connexin43, a gap junction protein which might play an essential role in decidua maturation. A decrease in the expression of that protein is linked with recurrent pregnancy loss.[41,43]

Furthermore, the expression of estrogen receptor alpha (ERα) and progesterone receptor A (PR-A) were confirmed on the surface of uterine TCs.[44] This suggests that TCs may be the sensors of sex hormone levels. TCs also express these receptors in uterine tubes and upper lamina propria of the human urinary tract.[45,46]

Additionally, human uterine TCs express 2 types of channels at their cell membrane: T-type calcium channels ($Ca_v3.1$, $Ca_v3.2$) and small-conductance calcium-activated potassium channels (SK3).[25]

The presence of $Ca_v3.1$ and $Ca_v3.2$ channels were confirmed both in cell body and Tps of TCs. Expression of $Ca_v3.1$ and $Ca_v3.2$ channels correlates with the reproductive state: $Ca_v3.1$ expression in pregnant and non-pregnant

Table 1. The variation in morphology of Tps and extracellular vesicles between non-pregnant and pregnant myometrium[31]

Parameter	Non-pregnant myometrium	Pregnant myometrium
Podom thickness [nm]	268.6 ±8.27	316.38 ±17.56
Podomer gauge [nm]	81.94 ±1.77	75.53 ±1.81
Number of exosomes/ shedded microvesicles	26/89	20/168
Diameter of extracellular vesicles [nm]	58–405 average 151	65–362 average 170

Table 2. Expression of markers on TCs in individual parts of female reproductive system

Organ	Marker							
	CD34	c-kit	vimentin	PDGFR-α	PDGFR-β	ERα	PR-A	Additional markers
Vagina	n/d	+	n/d	n/d	n/d	n/d	n/d	n/d
Uterus	+	+/–	+	+	+	+	+	α-SMA CD44 Sca-1
Uterine tubes	+	–	+	n/d	n/d	+	+	n/d
Ovaries	+	n/d	+	+	+	n/d	n/d	n/d
Mammary gland	+	+/–	+	n/d	n/d	n/d	n/d	CD10
Placenta	+	+	+	n/d	n/d	n/d	n/d	caveolin1

ERα – estrogen receptor α; PR-A – progesterone receptor A; n/d – no data.

state is equal, while $Ca_v3.2$ channels are mostly detected in pregnant myometrium.[25] Moreover, in non-pregnant state $Ca_v3.1$ were strongly expressed in Tps, while $Ca_v3.2$ were observed only in cell body. The differences in expression of these channels suggest that TCs may play role in detection of mechanical stretching of the pregnant uterus.[28]

SK3 channels were observed in the uterus of several species (for instance in human, mice or rat). Their expression is also correlated with pregnant or non-pregnant state. The density of SK3 channels in non-pregnant myometrium is elevated where they are present on TCs and vascular endothelium, in contrast to pregnant state with decreased number of channels, which are only located on vascular endothelium.[47] Downregulation of SK3 channels during pregnancy probably reduce contractility of the uterus. Changes in the expression of SK3 channels could also be caused by different stage of the hormonal cycle (expression of channels influenced by sex hormones) or diseases connected with hormonal imbalance.[29]

Uterine TCs create connections with other cells and components of extracellular matrix (for instance collagen or elastic fibres). Heterocellular junctions between TCs and smooth muscle cells, nerve endings and blood vessels were additionally observed.[48] TCs in uterus can also communicate by shedding membrane microvesicles: exosomes and ectosomes. No differences were noticed in number and diameter of shedded vesicles in pregnant myometrium compared with non-pregnant (Table 1).[25] Moreover, Diaz-Flores et al. proved that TCs have endocytic properties, which suggest existence of bidirectional information exchange between TCs and neighbouring cells.[49]

Additionally, TCs establish contacts with immune cells, namely lymphocytes, eosinophils, basophils, plasma cells, and macrophages.[38] Chi et al. confirmed that TCs are able to activate peritoneal macrophages, which may result in increased amount of IL-6, IL-10, IL1R1, TNF-α and iNOS. Pathologically high levels of these proteins could lead to implantation failure, immunologically-mediated abortion or endometriosis.[50]

TCs may also be useful in uterine regenerative medicine. Recent studies revealed that TCs from pregnant and non-pregnant myometrium have different reactivity to low-level laser stimulation (LSSS). Tps from pregnant uterus are more susceptible to extension after using LSSS compared to Tps from non-pregnant uterus. These differences are probably caused by variations in TCs' cytoskeleton structure (up-regulation of integrins) in pregnant and non-pregnant state.[51]

Telocytes in uterine tubes

TCs are located in lamina propria and muscular layer of uterine tubes. Their Tps create a 3-dimensional network between smooth muscle cells (SMCs), nerve endings and blood vessels. Close relations between TCs and SMCs may suggest that TCs participate in uterine tube contractility.[52]

TCs in the uterine tube present a typical cell phenotype. They shed 3 types of extracellular vesicles: exosomes (diameters: 60–100 nm), ectosomes (100–250 nm) and microvesicles (250–350 nm).[52] Similarly to the uterus, they express on their surface PR-A and ERα receptors, which might be connected with the control of peristaltic movements in the uterine tube due to changes in estrogen (acceleration of contractions) and progesterone (deceleration of contractions) levels.[1]

TCs are connected with other cells located in the uterine tubes tissue. Heterocellular junctions with fibrocytes, pericytes, SMCs, nerve endings, mast cells and stem cells were observed.[42] Yang et al. claimed that Tps are located in close vicinity to lymphocytes and plasma cells, which, according to their study, may suggest that TCs are involved in the stimulation of plasma cells to antibodies synthesis. However, the aforementioned property requires further investigation.[53]

Yang et al. proved that TCs' quantity and ultrastructure dramatically change in rat model of acute salpingitis. TCs retrieved from salpingitis-affected uterine tubes presented numerous abnormalities, such as: loss of organelles, cytoplasmic vacuolization, dilatation of rough endoplasmic reticulum and loss of intercellular junctions. Additionally, the number of TCs was significantly decreased.[53] The declined quantity of TCs, which is probably caused by the overproduction of iNOS, COX-2, LPO and estradiol, damages those cells and were also observed in pelvic endometriosis and tubal ectopic pregnancy.[40,42,54] Nevertheless, TCs of nearly normal appearance can be found even in endometriosis-affected uterine tube. Presumably, that is the reason why some women in this state have only reduced fertility instead of complete infertility.[42]

Telocytes in ovary

TCs were detected in the stroma of mice ovaries and they were positive for CD34, vimentin, PDGFR-α and -β. Thus far, the function of TCs in ovaries has not been determined; however, there is an assumption that they might be responsible for maintaining the local microenvironment.[55]

Liu et al. found statistically a significant decrease in the number of TCs in ovaries affected by cyclophosphamide-induced premature failure compared to healthy controls. As a consequence, they might be used as a marker of declining ovarian functions caused by the intake of cyclophosphamide.[55]

Telocytes in mammary gland

The existence of TCs in the mammary gland was confirmed in 2005 and they present morphology which is typical for them. They form a network of inactive mammary gland in the stroma, mainly in the interlobular space and also in the interlobular area, though in very small quantities. TCs closely encompass capillaries and mammary

gland ducts, predominantly by their Tps located perpendicularly to long axes of those structures.[56]

In mammary gland, TCs are positive for CD34 and vimentin.[57] However, there is an incongruity between the studies in terms of expression of c-kit – Gherghiceanu et al. along with Mou et al. confirmed the presence of that marker, while Petre et al. negated its expression.[56–58] Additionally, TCs in mammary gland might be partially positive for CD10.[58]

TCs are connected by stromal synapses with stromal immune cells, such as plasma cells, lymphocytes, mast cells and macrophages. Contacts with fibroblasts were also observed.[56] The direct link between TCs and endothelial cells or pericytes have not been found.[13]

Apart from the possible involvement of TCs in the organization of properly functioning structure of mammary gland, they may play an important role in the modulation of an immune system, thanks to their connections with immune cells.[56]

As accurate arrangement of stroma has a beneficial effect on maintaining local microenvironment, any alterations in the function of TCs' network may lead to an increase in the risk of neoplastic process in the tissue.[13] Mou et al. investigated the influence of TCs and other stromal cells on the growth dynamic of breast cancer.[57] They observed that TCs establish membrane-to-membrane connections with breast cancer cells in co-culture and presumably participate in the formation of neoplastic cell clusters. There was an increase in the proliferation index and a reduction in the apoptosis ratio among breast cancer cells accompanied by stromal cells, compared to isolated breast cancer cell culture.[57] Furthermore, the number of heterocellular junctions formed by TCs is diminished in neoplastic tissue.[13] Summing up, TCs along with other stromal cells may contribute to neoplasm development and survival.[57] As a consequence, TCs might emerge as a novel target in breast cancer therapy.

Telocytes in placenta

Placental TCs were detected by Suciu et al. in the large and peripheral stem villi, where they are located just beneath the trophoblast. Their Tps are orientated parallelly to the basement membrane and circularly or longitudinally to blood vessels.[21,40] They are positive here for: c-kit, CD34, vimentin, caveolin1, VEGF and iNOS.[25]

TCs create heterocellular contacts with mast cells, myofibroblasts, SMCs and specific placental macrophages, called Hofbauer cells (HBCs).[25] However, the function of TCs in human term placenta is still unknown. The presence of junctions between TCs and HBCs suggest their possible contribution to immune surveillance. Considering the fact that placenta is not an innervated organ, Bosco et al. suggested that TCs may be crucial for signal transduction resulting in blood flow in foetal vessels and aetiopathogenesis of pre-eclampsia.[59]

Conclusions

TCs are a unique cell population, located in the stroma of numerous organs, also in the female reproductive system. Their role specific for that system can be connected with their involvement in muscular layer contractility, pregnancy maintenance, immunomodulation and tissue regeneration. Alterations of their number in the female reproductive system might be connected with pre-eclampsia, endometriosis or acute salpingitis and further research on that subject may lead to a turning point in TCs-related treatment of those conditions.

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